REMARKS/ARGUMENTS

Claims 1, 5-9, 27-28, 32-36, and 64 have been amended to clarify that the protein being detected is encoded by SEQ ID NO. 16. Claims 1 and 28 have been amended to clarify that to indicate tumorigenicity, the ratio of positive cells to the total number of cells in a biological sample is greater than zero. Claim 27 has been amended to clarify that the presence of the protein encoded by SEQ ID NO. 16 in a biological sample is indicative of resistance to the antineoplastic effects of antiestrogens. No new matter is introduced by these amendments.

35 U.S.C. §112, Second Paragraph

Claims 1-12, 20-39, and 45-63 stand rejected as allegedly being indefinite under 35 U.S.C. § 112, second paragraph. Claims 1-12, 20, 21, 22, and 28 are allegedly "confusing" because the ratio of GP88 positive cells to negative cells could be from 0 to 1. Office Action at 4. In addition, according to the Office Action, "the specification, for example at page 52 Paragraph [00129], says that less than 5% GP88 positive cells is considered negative." Id. Claims 27, 29-39, and 45 are said to be "confusing" because the determining "amount of GP88" could be zero. Applicants have amended the present claims to more particularly point out the invention.

The Applicant's specification teaches that elevated levels of GP88 are indicative of tumorigenicity. See, e.g., page 48, paragraph 121. Page 52 of the specification describes a preferred grading scale for the amount of GP88 in a biological sample (the "intensity of GP88 staining in a biological sample is preferably graded as follows:"). Page 54 describes another preferred grading scale where "less than about 1% GP88 stained cells is considered negative or 0; about 1-5% GP88 stained cells is considered weakly positive for GP88 (1+); about 5-25% GP88 stained cells (2+) is considered moderately positive; and more than about 25% GP88 stained cells (3+) is considered strongly positive for GP88." However, the ratio can be lower depending on the sensitivity of the technique used for

detecting GP88. For example, the specification states that "the percentage of stained cells for each grade may be adjusted downward when using a more sensitive technique for detecting GP88 or when the biological sample pool is increased." Specification at page 54, paragraph 131.

In order to advance prosecution, and in accordance with the teachings of the specification, claims 1 and 28 have been amended to clarify that "a ratio greater than zero is indicative of resistance to the antineoplastic effects of antiestrogen therapy." Claim 27 has been amended to clarify that "the presence of GP88 is indicative of resistance to the antineoplastic effects of antiestrogen therapy." The claims as amended do not include zero. Therefore, this rejection should be withdrawn.

Claim 45 stands rejected under 35 U.S.C. § 112, second paragraph, for reciting the limitation "said number of GP positive cells." Claim 45 has been amended to remove the term "GP positive cells." Therefore, this rejection should be withdrawn.

Claim 46 stands rejected under 35 U.S.C. § 112, second paragraph, for reciting "said ratio" without antecedent basis. Claim 46 has been amended to depend from claim 28 and thus has antecedent basis for the term "said ratio." This rejection should therefore be withdrawn.

35 U.S.C. § 112, First Paragraph

Claims 1-12, 20-39, and 45-64 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly being non-enabled for "(1) ratio or amount of GP88 positive cells and (2) any other cancer." According to the Office Action, the specification "does not teach any other cancer could be diagnosed with the marker" or "present any in vivo data to correlate detection of the marker to growth of any tumor other than breast tumor." The Office Action alleges that to enable the claimed invention, the Applicant must show that "the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome" and "test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker

results with subsequent histological confirmation of disease." Office Action at 5-6. The Applicant respectfully traverses this rejection.

The Office Action alleges that the specification "does not teach any other cancer could be diagnosed with the marker." Id. This statement is incorrect. The specification teaches that the biological samples can be derived from a variety of tissue including, but not limited to "blood, cerebrospinal fluid, serum, plasma, urine, nipple aspirate, liver, kidney, breast, bone, bone marrow smears, testes, brain, ovary, skin, or lung." Specification at paragraph 125. The specification teaches that the "biological sample may be of any size, shape or tissue type and include any number of cells and/or cell types" and can "comprise non-tumorigenic cells and tumorigenic cells" or "biological fluid containing cells or tissue." Id. The specification teaches that elevated levels of GP88 in biological samples are indicative of tumorigenicity and resistance to the antineoplastic effects of antiestrogen therapy. See, e.g., Specification at paragraphs 121-131.

The specification teaches that GP88 is expressed in many tissue and cell types. For example, GP88 was originally identified by the Applicant as a highly tumorigenic, stringently required growth factor derived from a teratoma-derived adipogenic cell line 1246 (PC cells). Specification at paragraph 5, Figure 1. GP88 is expressed in mammary epithelial cells, fibroblasts, PC cells, human breast carcinoma, and human breast biopsies. See Figures 1, 12-21. Detailed description of methods for detecting GP88 and grading tumorigenicity and resistance to antiestrogen therapy based on GP88 levels are also provided. Id. The dramatic results of Applicant's claimed methods are clearly shown in Figures 3, 4, and 14-17 (elevated levels of GP88 indicate tumorigenicity) and Figures 21-23 (elevated levels of GP88 indicate resistance to the antineoplastic effects of antiestrogen therapy).

The Applicant's specification teaches one of skill in the art how to make and how to use the invention to diagnose tumorigenicity in a wide variety of tissues and fluids. The Applicant (1) has shown that GP88 is a highly tumorigenic growth factor expressed in a variety of cell types, (2) has fully and completely disclosed how to measure GP88 levels in

biological samples, and (3) has shown how to determine if the GP88 levels are indicative of tumorigenicity or resistance to antiestrogen therapy.

The Office Action sets forth a test for enablement that cannot be found in the MPEP, statutes, or caselaw. In order to meet the enablement requirement, according to the Office Action, Applicant must provide "in vivo," clinical data to correlate GP88 levels with tumorigenicity in tissues other than breast tissue. Office Action at 5. However, i*n vivo* data is not required to support enablement. While *in vivo* data may be required to obtain FDA approval for a diagnostic method, there is no such requirement in the patent law. As the Federal Circuit stated in In re Brana, "[t]he Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining governmental approval to market a particular drug for human consumption." In re Brana, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). Under the patent law, all that is required is a reasonable expectation that the claimed genus could be used as claimed without undue experimentation.

According to the MPEP, "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." MPEP § 2164.02. The MPEP says nothing about requiring *in vivo* data to support enablement. To the contrary, the test is whether one of skill in the art would expect the invention would work without undue experimentation. The specification more than meets this test.

Here, the specification demonstrates expression of GP88 in a variety of tissues and cells and provides a detailed description of methods for diagnosing tumorigenicity and resistance to antiestrogen therapy. To the extent any experimentation is needed to practice the invention using biological samples derived from tissues other than breast tissue, such experimentation is not undue. The factors considered to determine if undue experimentation is required include: the breadth of the claims; the nature of the invention;

the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. MPEP § 2164.01(a) (Eighth Edition).

The specification shows GP88 expression in a variety of tissue (e.g., teratoma, breast) and cell types (epithelial, carcinoma, breast, lung) and provides substantial direction for carrying out the claimed invention by detecting GP88 in a biological sample using a variety of techniques and reagents (e.g., immunohistochemistry, ELISA, Western Blot, Northern Blot). Moreover, the specification provides actual working examples of the invention including data generated from breast cancer patient biopsies. The presence or absence of GP88 in a given biological sample can be routinely determined by a person of skill in the art given the teachings of the specification. Thus, the quantity of experimentation required, if any, is low because there is a high level of predictability with regard to diagnosing tumorigenicity or resistance to antiestrogen therapy based on the working examples, data, and amount of direction provided by in the specification.

35 U.S.C. §103(a)

Claims 1-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Shoyab et al. (WO 91/15510). The Office Action states that Shoyab et al. "teach all of the necessary reagents used in the instant invention and teach the possible link between expression level of epithelin and cancer, one of ordinary skill in the art at the time of invention was make would have been motivated to determine if expression levels of epithelin could be used as a biomarker for cancer because cancer diagnosis using a biomarker is cheaper and faster." Office Action at 3. The Applicant respectfully traverses this rejection.

Several breakthrough discoveries by the Applicant provide the foundation of the claimed invention. Contrary to teachings of Shoyab et al., the Applicant discovered that GP88, the full length 88kDa precursor (encoded by SEQ ID 16) of Shoyab et al's epithelins, is a highly active and tumorigenic molecule. The Applicant discovered for the

first time that the full length epithelin precursor (GP88) is an active, stringently-required, overexpressed, and highly tumorigenic growth factor for tumor cells. The Applicant was also the first to show that elevated levels of GP88 indicate resistance to antineoplastic effects of antiestrogens.

Claim 1, as amended, is directed to diagnosing tumorigenicity in a human patient by "obtaining a biological sample containing cells from said patient; detecting the protein encoded by SEQ ID NO. 16 in said cells of said biological sample; determining the number of cells containing said protein in said sample; and determining the ratio of cells containing said protein to the total number of cells in said biological sample, wherein a ratio greater than zero is indicative of tumorigenicity." Claim 27 is directed to determining whether a patient is resistant to the antineoplastic effects of antiestrogen therapy by "detecting the presence of the protein encoded by SEQ ID NO. 16 in said sample wherein the presence of said protein is indicative of resistance to the antineoplastic effects of antiestrogen therapy."

Shoyab et al. teach that the epithelin precursor encoded by SEQ ID NO. 16 (GP88) is inactive. According to Shoyab et al., "[t]he unprocessed epithelin precursor has no activity in any of these assays[1]. Shoyab et al. ('510) at page 52, lines 13-18. Shoyab et al. were unable to confirm any activity of the unprocessed epithelin precursor (i.e., GP88). Shoyab et al.'s entire disclosure is directed to the processed 6kDa epithelins, the only biologically "active" molecules recognized by Shoyab et al. Thus, Shoyab et al. fail to teach detecting GP88 or determining the number of GP88 positive or negative cells in a biological sample. There is no disclosure or motivation based on Shoyab et al. to measure the level or expression of an "inactive" precursor.

Shoyab et al. also fail to teach diagnosing tumorigenicity wherein the ratio of GP88 positive to the total number of cells in a biological sample is greater than zero. Following the teachings of Shoyab et al. would lead, if anything, to the opposite of the

[1] The "assays" referred to by Shoyab et al. include assays for determining the biological effects of epithelins (e.g., the inhibitory effect of epithelin 1 on A431 cells, and mitogenic effect on normal cell lines). See Shoyab et al. '510 at page 52, lines 5-18.

claimed invention. According to Shoyab, epithelins (both epithelin 1 and epithelin 2) are tumor inhibitory molecules. Shoyab et al., ('510 patent) at page 27, lines 22-27. In contrast, Applicant's invention is based on the finding that the epithelin precursor (i.e., GP88) is a stringently required tumor growth stimulator. According to Shoyab et al., the epithelin precursor has no activity. The claimed invention diagnoses tumorigenicity by determining whether a biological sample has elevated levels of GP88. Based on Shoyab et al., one of skill in the art would have nothing suggestive of the claimed invention. Shoyab et al. teach that elevated levels of epithelins are indicative of tumor growth inhibition while the claimed invention requires that elevated levels of the protein encoded by SEQ ID NO. 16 are indicative of tumorigenicity.

Likewise, Shoyab et al. fail to provide motivation to practice the claimed invention. First, as discussed above, Shoyab et al. do not teach or suggest any diagnostic involving detecting the protein encoded by SEQ ID NO. 16 (GP88) which, according to Shoyab et al., is inactive. Rather, Shoyab et al. is directed exclusively to epithelins. Second, based on Shoyab et al. any motivation would be to practice the opposite of the claimed invention since, according to Shoyab et al., elevated levels of epithelins would indicate inhibition of tumorigenicity. There would be no reasonable expectation of success in practicing the claimed invention for these same reasons. Furthermore, Shoyab et al. does not contain a single word with regard to the relationship between resistance to the antineoplastic effects of antiestrogen therapy and the amount of the protein encoded by SEQ ID NO. 16 (GP88) present in a biological sample. Consequently, Shoyab et al. does not establish any of the three criteria necessary to establish a prima facie case of obviousness.

35 U.S.C. § 101 – Double Patenting

Applicant acknowledges the provisional obviousness-type double patenting rejection of claims 1-12, 20-26 in view of claims 20 and 28-56 of co-pending Application No. 09/456,886. Applicant will address the provisional rejection at the appropriate time when the allowable claims have been identified.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If Examiner Yu should believe that anything further may be required to place this application in even better form for allowance, she is cordially invited to telephone the undersigned attorneys for Applicant.

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Respectfully submitted,

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